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The role of circulating miR-200 family members in differentiating prostate cancer from benign prostatic hyperplasia

Mir-200 family in prostate cancer

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Abstract
Aim: Although prostate-specific antigen (PSA) is one of the best-known tumor markers used in the early diagnosis of prostate cancer, it may be insufficient in differentiating benign prostatic hyperplasia (BPH) from prostate cancer (PCa). In this study, in cases where the diagnostic power of PSA is insufficient, it was aimed to evaluate the possible diagnostic and prognostic roles of the miR-200 family (miR-200a, miR-200b, miR-200c, miR-141), which has been proven to be associated with cancer by many studies.
Material and Methods: Thirty-one untreated PCa patients were included in the study as the case group and 29 untreated BPH patients as a control group. PSA levels of all patient samples were measured. miRNAs expression levels were determined from total RNA isolated from plasma samples by the qRT-PCR method. The relationship between miRNAs and clinicopathological data was evaluated using statistical tests.
Results: The relative expression levels of the examined miRNAs, although not statistically significant, tended to decrease in the PCa group compared to the BPH group. The ability of miR-200 family members to differentiate PCa from BPH was found to be weaker than serum PSA, and no significant relationship was found between clinicopathological parameters and these miRNAs ($p>0.05$).
Discussion: Regardless of serum PSA, the potential of the circulating miR-200 family members to differentiate PCa from BPH is weak. Although our findings are guiding for future functional studies, it is thought that further studies should be done in larger patient groups.

Keywords
Prostate Cancer; Benign Prostate Hyperplasia; microRNA; microRNA-200 Family

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Introduction

Prostate cancer (PCa) is the most common malignancy of the male reproductive system worldwide [1]. The pathogenesis of PCa is still not fully understood; however, it is known to be a multifactorial disease involving genetic predisposition, hormonal changes and various environmental factors [2]. Although the most widely used biomarker that can correlate with the risk and prognosis of PCa is the prostate-specific antigen (PSA), benign prostatic hyperplasia (BPH), prostatitis, or the use of certain drugs can increase the PSA level and cause misdiagnosis in terms of PCa [3]. Therefore, non-invasive markers with higher sensitivity and specificity are needed in the early diagnosis of PCa. Recently, circulating microRNAs (miRNAs) have been proposed as potential new biomarkers for the diagnosis and prognosis of PCa [4].

Circulating miRNAs are known as promising diagnostic and prognostic biomarkers in various cancers, including PCa, due to their increased stability, tissue specificity, ease of detection, and frequent dysregulation during tumorigenesis [5, 6]. MiRNAs are short RNAs of 20-24 nucleotides that play a significant role in almost all biological processes in mammalian species [3]. While miRNAs can play the role of an oncogene when they target tumor suppressor genes, and similarly, when they target oncogenes, they can play a tumor suppressor role. Therefore, miRNA profiling has been a powerful tool to identify predictive miRNA signatures associated with the early diagnosis and progression of various cancers [7].

It has been determined that the miR-200 family (consisting of 5 miRNAs: miR-141/200a/200b/200c/429), which is a member of a certain microRNA family, plays a very significant role in tumor formation [8]. The role of miR-200 family members in cancer is considered mainly as tumor suppression [9]. Studies show that the miR-200 family plays a significant role in epithelial-mesenchymal transition (EMT), migration, apoptosis, tumor cell adhesion, and regulation of angiogenesis [9, 10]. However, the available data suggest that the biological functions of the miR-200 family may differ depending on the stage of tumor progression and metastasis, and the nuclear or cytoplasmic localization of the interacting targets [9].

In our study, it was aimed to reveal the power of expression levels of miR-200 family members in the differential diagnosis of PCa and BPH in cases where serum PSA was insufficient, and to determine their roles in the pathogenesis and severity of the disease. Besides, in this study, which aims to determine their role as a non-invasive biomarker in the development and progression of PCa, their relationship with clinicopathological parameters was also examined.

Material and Methods

Study design and samples collection

The research protocol was created following the Declaration of Helsinki, and it was reviewed, approved and registered by the Ethics Committee of Süleyman Demirel University Faculty of Medicine (dated 29.03.2018, with the decision no. 2018/65). All patients were evaluated in the Urology policlinic of the SDU hospital. The study included 31 untreated PCa and 29 BPH patients. All patients provided written informed consent. Patients with different malignancies, chronic diseases and inflammatory diseases other than PCa and BPH were excluded from the study. A healthy control group was randomly selected from individuals without any systemic disease and drug use. All medical histories of the patients were questioned and recorded. PCa patients were subjected to clinical evaluation to determine the stage of prostate cancer. The stage of PCa was evaluated by the tumor node metastasis (TNM) system according to the American Joint Committee on Cancer. PCa grading was made according to the Gleason score. If PSA<10 ng/mL and GS<7 were considered as low risk, if PSA is 10-20 ng/mL and GS=7 as a medium risk, if PSA>20 ng/mL and GS>7 as high risk. Venous blood (4cc) was drawn into EDTA tubes from the patients. The collected blood was centrifuged for 10 minutes at 15,000 rpm in 1 hour in a cooled centrifuge and the plasma samples were stored at -80°C. The chemiluminescence immunochemical method (Beckman Coulter) was used to determine serum concentrations of total specific antigen (tPSA) and free PSA (fPSA).

Selection of candidate miRNAs and primer sequences

Candidate miRNAs, assumed to target genes associated with PCa, were selected using insilico tools. TargetScan Release 7.2 (http://www.targetscan.org/vert_72/) and miRDB (http://mirdb.org/index.html) algorithms were used for this purpose. The primer sequences of the miRNAs we researched are given in Table 1.

RNA isolation and cDNA synthesis

Total miRNA was isolated using the Hybrid-RTM miRNA Isolation Kit (GeneAll Biotechnology, Korea) following the manufacturer's instructions. miRNA samples with a sufficient quantity and high quality were used. Measurements of the isolated total miRNAs were made with the Thermo Fisher NanoDrop™ spectrophotometer device. Samples with an A260/280 ratio below 1.8 or A260/230 ratio below 2.0 were not included in the study. From the obtained total miRNA, using the WizScript™ cDNA Synthesis Kit, cDNA was obtained using the stem-loop primer separately for each miRNA to be studied. Reverse transcription was performed using SimpliAmp Thermal Cycler (Thermo Fisher Scientific, US). cDNA samples were stored at -80ºC until Real-Time PCR analysis was performed.

Quantitative PCR analysis

The quantitation of miRNA molecules was performed using the StepOnePlus Real-Time PCR Detection System (Thermo Fisher Scientific, US). RT-PCR steps were performed according to the manufacturer's instructions. The expression of the selected miRNAs in the blood was normalized to the expression of U6 small nuclear RNA (RNU6B). Each experiment was performed at least in duplicate.

Statistical analysis

Statistical analysis was performed using PASW (Predictive Analytics SoftWare) version 19 program. Continuous variables were expressed as mean ±SD, and the level of significance was defined as $p<0.05$. Normality test was done using the Kolmogorov-Smirnov test. It is compared using an independent sample t-test for normally distributed data and a Mann-Whitney U test for non-normally distributed data. Comparison of categorical data was made using the chi-square test. Specificity and sensitivity were combined in receiver operating characteristic (ROC) curve analysis and reported in areas under

the curves (AUCs). Fold change analysis between groups was performed using the Relative Expression Software Tool (REST 2009, version 1, released 22).

Results

Demographic data of the study subjects

The patient's clinical and demographic data are listed in Table 2. The mean age of the PCa patients was 68.13±7.88 years, while the mean age of BPH patients was 65.48±7.61 years; there was no significant difference between the studied groups regarding the age (p=0.192), so the two groups were well matched in terms of age. Serum PSA levels were significantly higher in the PCa group (p=0.000). It was found that 38.7% of the patients had GS<7, 19.4% of them had GS=7, and 41.9% of them had GS>7. According to clinical staging, T1c was determined as 3.2%, T2a was determined as 16.1%, T2b was determined as 6.5%, T2c was determined as 12.9%, T3a was determined as 16.1% and metastasis status was determined as 45.2%.

Table 1. The primer sequences of the detected miRNA

Gene	Primer sequence	GenBank Accession Number
miR-200a-3p	F 5'- CATCTTACCGGACAGTGCTGGA R 5'- CGAGGAAGAAGACGGAAGAAT	MIMAT0000682
miR-200b-3p	F 5'- TAATACTGCCTGGTAATGATGA R 5'- CGAGGAAGAAGACGGAAGAAT	MIMAT0000318
miR-200c-3p	F 5'- CGTCTTACCCAGCAGTGTTTGG R 5'- CGAGGAAGAAGACGGAAGAAT	MIMAT0000617
miR-141-3p	F 5'- CATCTTCCAGTACAGTGTTGGA R 5'- CGAGGAAGAAGACGGAAGAAT	MIMAT0000432
RNU6B	F 5'- GCTTCGGCAGCACATATACTAAAAT R 5'- CGCTTCACGAATTTGCGTGTCAT	NR_002752

Table 2. Clinical and demographic data of subjects involved in the study

	PCa	BPH	p-value*
N	31	29	-
Mean Age, years	68.13±7.88	65.48±7.61	0.192
Mean PSA, ng/mL	34.48±38.18	4.73±3.73	0.000
Serum PSA, n(%)			
0-4 ng/mL	0	16(%55.2)	0.000
4-10 ng/mL	13(%41.9)	11(%37.9)	
>10 ng/mL	18(%58.1)	2(%6.9)	-
Gleason Score (GS)			
<7	12(%38.7)	-	-
=7	6(%19.4)	-	
>7	13(%41.9)	-	
Clinical Stage, n(%)			
T1c	1(%3.2)	-	
T2a	5(%16.1)	-	
T2b	2(%6.5)	-	
T2c	4(%12.9)	-	
T3a	5(%16.1)	-	
M	14(%45.2)		

Data are expressed as mean ± SD. * p <0.05, statistically significant. PCa; prostate cancer, BPH; benign prostatic hyperplasia, PSA; prostate-specific antigen. T; Tumor, M; Metastasis.

Table 3. Plasma expression of miRNAs in patient groups

	FC	Std. Error	95%CI	p value*
miR-200a-3p	0.816	0.058 - 8.254	0.003 - 246.766	0.776
miR-200b-3p	0.615	0.070 - 5.034	0.014 - 82.952	0.442
miR-200c-3p	0.434	0.050 - 6.807	0.000 - 99.455	0.297
miR-141-3p	0.737	0.016 - 23.132	0.000 - 198.602.743	0.754
RNU6B	1	0.073 - 10.336	0.008 - 4.433.300	1

*p<0.05, statistically significant. FC; fold change. Expression coefficients of candidate miRNAs in PCa and BPH patients were calculated using the Relative Expression Software Tool (REST 2009).

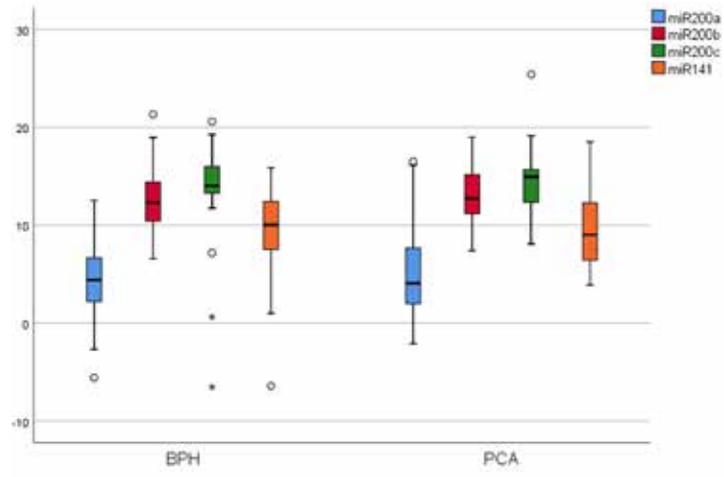

Figure 1. Box plots of miRNAs with different expression levels in PCa and BPH patients. BPH; benign prostate hyperplasia, PCa; prostate cancer.

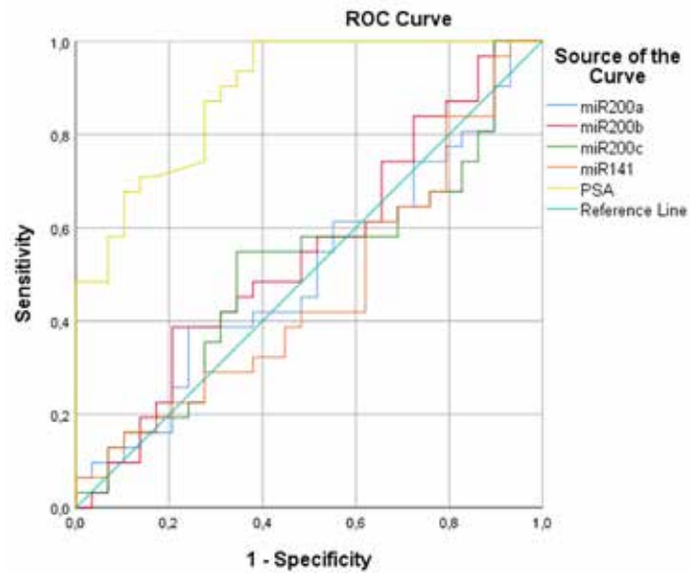

Figure 2. The ROC curve analysis of miRNA and PSA levels to differentiate PCa patients from BPH. ROC: receiver operating characteristic. Sensitivity, specificity (both with 95% CI), AUC and cut-off values of normalized miRNA expressions at log2 (2-ΔΔCT) were determined by ROC analysis.

Plasma expressions of miRNAs

MiRNA expression was determined in plasma samples of PCa and BPH patients using qPCR relative to the endogenous control RNU6B. Values were expressed as relative median fold change in gene expression. Target miRNAs and RNU6B established reliable Ct values in plasma samples of PC and BPH patients. The expression of miRNAs showed a downward trend in the PCa group compared to the BPH group, although it was not statistically significant. The fold changes of miR-200a, miR-200b, miR-200c and miR-141 in the PCa group, compared to the BPH group were 0.816, 0.615, 0.434 and 0.737, respectively. Fold changes and expression distributions between groups are given in Table 3 and Figure 1.

Relationship Between miRNA Levels and Clinical Data

In our study, the relationship of features such as serum PSA, Gleason score, and clinical staging with miRNA expression levels was researched. There was no significant correlation between serum PSA and miR200a, miR200b, miR200c or miR141 expression levels (r=0.109, p=0.406; r=-0.24, p=0.857; r=-0.27, p=0.836, r=-0.58, p=0.658 respectively.). In addition, there was no significant difference between the Gleason score and clinical staging or miRNA expression levels (p=0.829, p=0.268, p=0.827, p=0.767, respectively).

miRNAs and serum PSA as diagnostic markers

ROC analyzes were performed to evaluate the value of circulating miRNAs as a diagnostic marker for PCa. ROC curves are given in Figure 2. The area under curve (AUCs) value, which was used to distinguish prostate cancer from the BPH group, was found as 0.505 for miR-200a, 0.548 for miR-200b, 0.509 for miR-200c, 0.465 for miR-141, and 0.890 for PSA. The sensitivity and specificity of these miRNAs, were determined as 54.8% and 48.3% for miR-200a, 54.8% and 51.7% for miR-200b, 54.8% and 65.5% for miR-200c, 41.9% and 51.7% for miR-141, 87.1% and 72.4% for PSA, respectively. The power of miRNAs to differentiate PCa from BPH was not statistically significant. However, the diagnostic power, sensitivity and specificity values of serum PSA were significant.

Discussion

Prostate cancer is among the most common cancers in the world and the leading cause of cancer death in men. BPH, which is common in men, affects about 70% of men over the age of 70 [11]. Unfortunately, BPH is often misdiagnosed, thus leading to invasive prostate biopsies for differential diagnosis when not needed [12]. Therefore, alternative non-invasive biomarkers have become important to help in the early diagnosis of PCa, as well as to differentiate patients with malignant and benign prostates and reduce the need for invasive biopsies [3]. miRNAs play an important role in tumor development due to their ability as regulators of tumor suppressor genes and to act as oncogenes [13]. With the discovery of these features, miRNAs have been considered ideal non-invasive biomarkers in many types of cancer [14].

This study aimed to determine the circulating miRNAs that differentiate PCa from BPH in the patient population with increased PSA levels. Besides, it was aimed to determine the roles of the circulating miR-200 family in the pathogenesis of PCa and BPH, and to evaluate their diagnostic and prognostic roles. In our study, the relative expression levels of miRNAs showed a downward trend in the PCa group compared to the BPH group, although it was not statistically significant. No significant difference was found between other clinicopathological parameters and miRNA expression levels. Besides, the ROC analysis, which evaluated the diagnostic powers for the differentiation of BPH and PCa, did not find miRNA with a higher diagnostic power than PSA was detected. Studies have shown that miR-200 family members are abnormally expressed in many human malignancies, and these miRNAs play a role in tumor pathogenesis during the carcinogenesis process. It is known that miR-200 family members are downregulated during the tumor progression process [15]. Additionally, the miR-200 family is a tumor suppressor microRNA family that plays critical roles in suppressing EMT [16].

miR-200a and miR-141 are known to inhibit migration, invasion, proliferation and drug resistance in various forms of cancer [17]. miR-141 is dysregulated in malignant tumors and plays an important role in tumor development and progression [17]. Agaoglu et al., in their study, to differentiate PCa patients that have metastasis from those who have locally advanced disease, reported that miR-141 was the strongest differentiator of metastatic PCa in clinical practice, supporting PSA testing [14]. Zhang et al. suggested that the miR-141 expression level increased in the serum of patients with bone-metastatic prostate cancer and positively correlated with bone lesions [18]. In the study conducted by Brase et al., high levels of circulating miR-141 were found to be associated with high-risk (Gleason score≥8) tumors, while low levels of miR-200a were found to correlate with recurrence in prostate cancer [19]. While Barron et al. pointed out that measuring miR-200a on its own in patients with prostate cancer would not have sufficient sensitivity and specificity to be useful for predicting recurrence, they stated that miR-200a could be a part of a panel of biomarkers with other family members [20]. Akbayır et al. researched miRNA expression values in order to increase the diagnostic power of the grey zone PSA in PCa and BPH patients, and they found no significant difference between the groups in terms of miR-141 expression [21]. In our study, compatible with Akbayır et al., miR-141 and miR-200a expressions were found to be downregulated in the cancer group, although this was not statistically significant (FC=0.737, p=0.754, FC=0.816, p=0.776, respectively). We think that this downregulation can facilitate cancer progression by inducing EMT, the first step of metastasis, similar to the study of Du et al. [22]. However, the weakness of miR-141 and miR-200a in differential diagnosis compared to serum PSA (AUC = 0.465, AUC = 0.505, respectively) made us think that these miRNAs could not help to improve the diagnostic prediction.

miR-200b and miR-200c are important regulators of epithelial-mesenchymal transformation. In addition to its role in normal cell phenotypic transformation, miR-200b/200c is differentially expressed in many cancer cells. However, there are few studies in the literature regarding miR-200b/200c and PCa, and it is unclear whether they regulate PCa [23]. Zhang et al. found that the tumor suppressor miR200b is overexpressed in human prostate tumors [24]. Vrba et al. showed that miR-200c is less expressed in normal prostate tissues compared to cancerous

tissues [25]. Yu et al. found that miR-200b expression was significantly downregulated in PCa tissues compared to BPH tissue samples [8]. In our study, we found that the expression levels of miR-200b and miR-200c decreased in the cancer group, although it was not statistically significant (FC=0.615, p=0.442, FC=0.434, p=0.297, respectively). Our findings suggest that these downregulated miRNAs may play a vital role as a potential tumor suppressor in PCa tumor development and progression. However, the weakness of miR-200b and miR-200c in differential diagnosis compared to serum PSA (AUC = 0.548, AUC = 0.509, respectively) showed us that these miRNAs cannot be independent biomarkers.

In miRNA expression profiling studies carried out to differentiate prostate cancer from BPH, there may be contradictions due to many reasons, such as the use of different samples (such as tissue, plasma, urine, serum), the inclusion of populations of different sizes in the study, the difference in expression profiling methods, the selection of patients with BPH or healthy volunteers as a control group. Although our findings serve as a guide for future functional studies, they are limited due to their small population and the evaluation of a small number of miRNAs.

As a result, plasma expression levels of the miR-200 family tended to decrease in the group with PCa compared to the group with BPH. Independently of serum PSA, these molecules did not have sufficient sensitivity and specificity to be useful for distinguishing PCa from BPH. It is thought that the present study should be conducted in a larger population in a multicenter group to evaluate the roles, potential diagnostic and prognostic roles of circulating miR-200 family expressions in carcinogenesis as non-invasive biomarkers for PCa.

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Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest
None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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